## REMARKS

Claims 1-3, 6, 10-20, 23, 26-29 and 32 are pending and under consideration in the present application. Applicant has amended claim 26, but no new matter has been added.

### 1. Section 112, Second Paragraph Rejection: Alleged Indefiniteness

Claim 26 was rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. Claim 26 was rejected because it included a reference to "said catalytic antibody" which lacks antecedent basis. (Office Action, p. 2).

Applicant has amended claim 26 to refer to an enzyme rather than a catalytic antibody. Favorable reconsideration and withdrawal of the Section 112, second paragraph, rejection are requested.

### 2. Section 112, First Paragraph Rejection: Alleged Lack of Written Description

Claims 1-3, 6, 10-20, 23, 26-29 and 32 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in a way that conveys that the inventor(s) had possession of the claimed invention as of the filing date. (Office Action, pp. 2-3). The Examiner argues that the specification fails to describe the physical and/or chemical properties of the claimed class of target molecules and their corresponding biological function, the label and the transition state analog. (*Id.* at pp. 3-4).

Applicant respectfully traverses and submits that the specification provides ample disclosure to reveal to the skilled artisan that the Applicant was in possession of the claimed invention as of the filing date. At page 7 et seq. the specification explains that the target substance is preferably a biological substance, such as a protein, nucleic acid, carbohydrate, cell, subcellular particle, prion, virus, phospholipids, etc., and/or a substance with a particular biological activity, e.g., a receptor, ligand, hormone, gene, gene message, enzyme, cytokine, etc. The biological substance can be natural or synthetic (see page 7, lines 6-10) and preferably, the

target molecule has a biological activity that is relevant to a disease state so that inactivation or modulation of that biological activity has therapeutic relevance. A non-limiting list of biological targets that may be used in the method of the present invention includes TNFα, IL-4, IL-6, VEGFr2, CD3ε, IL-l, TGF-β, gp120, IgE CD45, CD33, EGF receptor, CD20, CD40, HER2/neu, HER2 receptor, TNFα receptor, VEGF, 2B1, IgE, ICAM-1, CD6, CD18, hCG, CD25, IL-2, IL-2 receptor, CD58, α4-integrin, β2 integrin, A4b7 integrin, FcγR1, TAG-72, hepatitis B virus, DNA Histone H1 complex, gpIIbIIIA, ICAM-3, CD4, CD11, CD18, CD28, CD2, CD80, CD48, HLA-Dr10, CBL, respiratory syncytial virus, CD52, IL-8, and CA125 (see page 7, lines 16-22). Specific target proteins are discussed at length in the specification, and that disclosure includes specific information concerning the biological structure and function of each representative target protein, i.e., TNFα, pages 20-22, VEGFr2, pages 22-23, IL-4, pages 23-24, IL-6, pages 24-25, CD3ε, page 25-28.

The specification also explains that the catalyst is a substance that catalyzes the modification and, preferably, the labeling of the target substance, e.g., enzymes, catalytic antibodies, and catalytic nucleic acids (see page 7, line 23, to page 8, line 21). The label is described in the specification as any chemical group or moiety that can be linked to the target substance, e.g., a detectable label that is suitable for the sensitive detection of the target substance. A non-limiting list of detectable labels that may be used in the claimed method and compositions includes luminescent labels, radioactive labels, enzymes, particles, magnetic substances, electroactive species and the like. Alternatively, a detectable label may signal its presence by participating in a specific binding reaction, e.g., haptens, antibodies, biotin, streptavidin, his-tag, nitrilotriacetic acid, glutathione S-transferase, glutathione and the like. In another embodiment, the label need not be detectable, but instead functions to modulate the biological activity of the target substance, e.g., the attachment of one or more labels to the target

may interfere with the activities of an active site on the substance or it may prevent the recognition of the target substance by a binding partner of the target substance. In yet another embodiment, the label may be a signaling moiety that targets the target substance for degradation, e.g., ubiquitin, or that targets the substance for transport, e.g., to a specific tissue or region of a cell. More detail regarding the nature of the label can be found in the instant specification, inter alia, at page 8 et seq.

In the Examples, the specification first describes experiments that were conducted to determine whether catalytic antibodies can chemically modify and thereby inactivate disease-associated proteins. The reaction of reducing sugars with TNFα was examined (page 35 et seq.). The reducing sugar aldehyde covalently reacts with lysine sidechains within the protein and that chemical modification was detected using an ECL-based binding assay that measures the binding of TNFα to its receptor. It was found that sugars gradually inactivate the receptor function over a 2-week incubation period, whereas the non-reducing sugar, sucrose, did not inactivate that biological function.

The uncatalyzed reaction between a β-lactam (ampicillin) and two proteins was also examined. Bovine serum albumin (BSA) and ampicillin were reacted overnight, and it was found that ampicillin groups were covalently attached to BSA. Ampicillin was also reacted with TNFα overnight. It was found that ampicillin caused a 16% loss of TNFα biological activity (according to the receptor binding assay). This reaction is much more facile than the reaction of TNFα with reducing sugars. This work shows that β-lactam antibiotics are effective modification labels in the inactivation of therapeutically-relevant target proteins. (See Example 1, which describes experiments that show the use of catalytic antibodies to inactivate disease-associated proteins; see Examples 2-5, which describe the panning of a human phage antibody repertoire display library against an antibiotic-target protein complex and the use of the resulting

subset of antibodies in HTS and directed evolution, wherein the target molecule is TNFα, VEGFr2, IL-4, and IL-6.

The MPEP clearly states that "a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention." See, e.g., *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563, 19 USPQ2d 1111, 1116 (Fed. Cir. 1991). An applicant shows possession of an invention "by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention." *Lockwood v. American Airlines, Inc.,* 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997). "Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. See, e.g., *Pfaff v. Wells Electronics, Inc.*, 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406; *Amgen, Inc. v. Chugai Pharmaceutical*, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991) (one must define a compound by "whatever characteristics sufficiently distinguish it")." (MPEP § 2163(I)).

Applicant submits that the claimed method is described in the specification as outlined above in sufficient detail to satisfy the requirements of the first paragraph of 35 U.S.C. § 112. (See MPEP § 2163.02, "Standard for Determining Compliance with the Written Description Requirement"). When one considers the high degree of skill in the art, one will readily appreciate that the Applicant has provided sufficient details regarding the target molecule, the

label, the enzyme or catalytic antibody and the remaining elements and defining characteristics of the claimed invention to distinguish the invention.

The MPEP clearly states:

> The inquiry into whether the description requirement is met must be determined on a case-by-case basis and is a question of fact. *In re Wertheim*, 541 F.2d 257, 262, 191 USPQ 90, 96 (CCPA 1976). A description as filed is presumed to be adequate, unless or until sufficient evidence or reasoning to the contrary has been presented by the examiner to rebut the presumption. See, e.g., *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). The examiner, therefore, must have a reasonable basis to challenge the adequacy of the written description. **The examiner has the initial burden of presenting by a preponderance of evidence why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims.** *Wertheim*, 541 F.2d at 263, 191 USPQ at 97.

(MPEP § 2163.04, emphasis added.).

Applicant respectfully submits that the Examiner has not met his burden. The Examiner takes issue with the breadth of the instant claims, without reasonably considering whether that breadth is supported by the instant specification in context, i.e., would one skilled in the art recognize in the instant disclosure a description of the invention defined by the claims. Contrary to the Examiner's assertions, the present specification provides extensive disclosure of the claimed invention. Still further, the level of skill in the art is high, such that given the extensive disclosure in the specification, the skilled artisan would readily appreciate how to apply the instant invention to other systems.

"In claims involving chemical materials, generic formulae usually indicate with specificity what the generic claims encompass. One skilled in the art can distinguish such a

formula from others and can identify many of the species that the claims encompass. Accordingly, such a formula is normally an adequate description of the claimed genus." *Reagents of the University of California v. Eli Lilly*, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997); MPEP § 2163 (III-3(a)), page 2100-179, left-hand column). Still further, MPEP § 2163 (III-3(a)) clearly states that "although structural formulas provide a convenient method of demonstrating possession of specific molecules, other identifying characteristics or combinations of characteristics may demonstrate the requisite possession." As explained by the Federal Circuit, "there is no per se rule that an adequate written description of an invention that involves a biological macromolecule must contain a recitation of known structure." *Falkner v. Inglis*, 448 F.3d 1357, 1366, 79 USPQ2d 1001, 1007 (Fed. Cir. 2006). See also *Capon v. Eshhar*, 418 F.3d 1349, 1358, 76 USPQ2d 1078, 1084 ("The Board erred in holding that the specifications do not meet the written description requirement because they do not reiterate the structure or formula or chemical name for the nucleotide sequences of the claimed chimeric genes" where the genes were novel combinations of known DNA segments.). For example, a disclosure of unique cleavage by particular enzymes, isoelectric points of fragments, detailed restriction enzyme maps, a comparison of enzymatic activities, or antibody cross-reactivity may be sufficient to show possession of the claimed invention to one of skill in the art. See *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966 ("written description" requirement may be satisfied by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that fully set forth the claimed invention"). (MPEP § 2163-III-3(a)).

Applicant respectfully submits that it is improper to reject claims on the ground that the specification does not support the claims when the terms of the claim are no broader than the broadest description of the invention in the specification and there is no reason to challenge the

operativeness of the subject matter embraced by the claims. *Ex parte Altermatt*, 183 USPQ 436 (POBA 1974).

Thus, one of ordinary skill in the art would readily recognize from the original disclosure that Applicant invented the presently claimed subject matter. Applicant submits that the Examiner's allegation that the specification is deficient in that it does not show working examples is not relevant to a determination of whether Applicant has satisfied the written description requirement of the first paragraph of 35 U.S.C. § 112.

In view of the foregoing remarks, Applicant respectfully submits that the written description rejection should be withdrawn.

**3. Rejection Under Section 112, First Paragraph: Alleged Lack of Enablement**

Claims 1-3, 6, 10-20, 23, 26-29 and 32 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly non-enabled. The Examiner alleges that the specification does not enable the skilled artisan to make and use the claimed invention. (Office Action, pp. 6-10). Applicant traverses for the reasons of record and those provided below.

MPEP § 2164.01 (a) enumerates a number of factors for determining whether experimentation is undue. The Applicant asserts that considering all of these factors the experimentation inherent in antibody generation and in the generation of antibodies according to the invention is not undue. In the instant specification there is considerable detail, direction and guidance, for generating antibodies as claimed. The extensive disclosure is outlined above in great detail and the skill in the art is high. When the disclosure is given careful consideration by a skilled artisan, it would be apparent that the quantity of experimentation required to reduce the invention to practice is not undue.

Enablement is not precluded by the necessity for some experimentation such as routine screening, Instead, experimentation needed to practice the invention must not be undue

experimentation. The key word is "undue" not "experimentation." "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." See e.g., MPEP § 2164.06. "The test for enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation." A patent may be enabling even though some experimentation is necessary. *United States v. Telectronics, Inc.* 857 F.2d 778, 8 USPQ2d 1217 (Fed. Cir. 1988), *cert. denied*, 490 U.S. 1046 (1989).

The generation of antibodies such as those used in the claimed methods, like the generation of conventional antibodies requires a certain amount of experimentation to screen for antibodies with the appropriate activity and may not always be successful. In *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988), the Federal Circuit held that such experimentation, when carried out for generation of conventional monoclonal antibodies, is reasonable and not undue because of the high level of skill in the pertinent art and, also, because of the considerable direction and guidance provided in the specification on how to practice the invention.

Moreover, working examples are not required to satisfy the enablement requirement. (MPEP § 2164.02). Although the Examiner may prefer working examples, the preference does provide a substitute for current legal standards of patentability. The specification provides extensive disclosure of the methods of making and using catalytic antibodies, as well as target molecules to be modified by disclosed antibodies. Every stage of the process is disclosed in great detail, thus enabling a person of ordinary skill in the art to practice the claimed invention without undue experimentation. The disclosure also teaches how to test the antibodies for the desired activity, e.g., catalytic antibody can be identified by screening human phage antibody

display libraries against an antibiotic-target conjugate. The specification teaches selecting labels that exhibit a low but detectable reaction with the desired target in the absence of a catalyst, for example, the conjugation reaction of β-lactam antibiotics with proteins (Specification, page 9, line 15 – page 10, line 10). The same passage in the specification also notes that the fact that the uncatalyzed reaction can occur at a slow rate places a lower burden on the catalyst and may only require that the catalyst bind to both the target and label so as to hold them in close proximity and increase their effective concentrations. In addition, the specification is not limited to selection of catalytic antibodies by panning phages and also teaches a variety of other approaches including directed evolution under selective pressure and/or the mutation of catalysts with similar chemical activities but different structural specificity. The fact that the specification does not provide working examples of the elicitation of catalytic antibodies does not support the Examiner's rejection.

Contrary to the Examiner's suggestion, the specification need not provide examples or specific description of embodiments for the entire scope of the invention. Detailed procedures for making and using an invention may not be necessary if the description of the invention itself is sufficient to permit those skilled in the art to make and use the invention. (MPEP § 2164). "A patent does not teach, **and preferably omits**, what is well known in the art. *In re Buchner*, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81, 94 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987); *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984)." (MPEP § 2164.01, emphasis added).

Moreover, the Applicant has previously submitted evidence regarding the advanced level of skill in the relevant art (see Applicant's arguments regarding Nevinsky et al., and Stevenson et al.).

Applicant maintains that the claims are fully enabled by the disclosure and further in view of the high state of relevant art. Favorable reconsideration is earnestly solicited.

**4. Rejection Under 35 U.S.C. § 102(b): Alleged Anticipation**

Claims 17-20, 23, 26-29 and 32 were rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Tanaka et al. (Tet. Lett. (1999): 8063-66) ("Tanaka"). The Examiner alleged that Tanaka teaches a catalytic antibody that assists in the formation of an acyl-enzyme bond between beta-lactamase (as the alleged target) and a β-lactam-type compound (as the label). (Office Action, p. 10).

Applicant respectfully disagrees. A claim is anticipated only if each and every element of the claim is found, either expressly or inherently, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987). The instant claims are directed to modifying a target molecule by attaching a label, thereby modulating an activity of the target, deactivating the target molecule, or targeting the molecule for degradation or clearance.

Tanaka does not teach or suggest all of the claimed limitations. Accordingly, withdrawal of the Section 102 rejection is respectfully requested.

## CONCLUSION

In view of the foregoing amendment and remarks, reconsideration of Claims 1-3, 6, 10-20, 23, 26-29 and 32 pending in this application and allowance are earnestly solicited.

No additional fees are believed due except for the fee for a three-month extension of time. However, the Commissioner is hereby authorized to charge any required fees and credit any overpayments to **Deposit Account No. 50-0540**.

Dated: March 4, 2008

Respectfully submitted,

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